

CRT Licensing Opportunity



Leptin Antagonists as Cancer Therapeutics

- Novel peptide based leptin receptor antagonists with nanomolar IC₅₀'s in proliferation assays
- *In vivo* efficacy demonstrated in ER+ and ER- xenografts and in an endometriosis model
- No signs of toxicity or effects on body weight in mice following 30days of treatment
- CRT funded peptide optimisation programme ongoing

BIOLOGICAL THERAPEUTICS | *In Vivo* Proof-of-Principle

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Indications

Initially breast cancer, but with potential in colorectal, endometrial, liver, gastric and esophageal cancers.

Endometriosis.

Inventors

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Background

Breast cancer is one of the most prevalent tumour types with over 440,000 new cases occurring annually in the 7 major pharmaceutical markets. Despite the availability of well known therapies such as anti-oestrogens, Herceptin™ and aromatase inhibitors the mortality rate remains at around 20% per year.

Over the last 5 to 10 years evidence has been accumulating that leptin signalling may play an important role in the development and maintenance of breast and other cancers (1). Studies of clinical tumour samples indicate that both leptin and the leptin receptor are frequently over expressed in breast tumour cells (92% and 83% of cases respectively). Over expression was in evidence across a range of breast tumour stages (TNM1-4) and across tumours with differing receptor status (ER+/- and Her2+/-) (2).

Leptin has been shown to promote the proliferation of a wide range of cancer cell lines and genetic studies have shown that

leptin signalling is absolutely required for tumour development in the MMTV-TGF- α driven spontaneous tumour model (3).

Clinical studies have suggested that increased levels of leptin may be associated with breast cancer and it has been proposed in the literature that excessive leptin signalling may contribute to the link between obesity and cancer.

Technology

Modelling studies by the inventors identified two helices of the leptin protein involved in binding to the leptin receptor. Synthesis and testing of peptides derived from these helices lead to the discovery of potent receptor antagonists (4). Cellular studies with these peptides indicated that they inhibit leptin signalling pathway activation and also leptin induced VEGF expression (5). Further cellular studies demonstrated that the peptide antagonists inhibit cancer cell proliferation with nanomolar IC₅₀'s and inhibit angiogenesis in the chicken chorioallantoic membrane assay.

With peptide based therapeutics the *in vivo* half-life can often be an issue. To address this problem the inventors generated pegylated versions of the peptides which were shown to retain full activity and to have an *in vivo* half-life greater than 18 hours.

On the back of these promising experiments the efficacy of the peptides was tested in a number of breast tumour models. In the murine 4T1 syngeneic model, administration of the peptides reduced tumour growth by 50-90% over the 3 week experimental period (5).

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Further xenograft testing using the human MCF7 breast cancer cell line again produced impressive anti-tumour activity. In this instance treatment every second day by intravenous injection was instigated only after tumours were established. In this experiment the antagonists resulted in a substantial reduction in tumour size with tumours barely detectable in the treated group at the 3 week endpoint (see figure 1) (6). The leptin antagonist peptides were also able to inhibit growth of Er-xenografts (6).

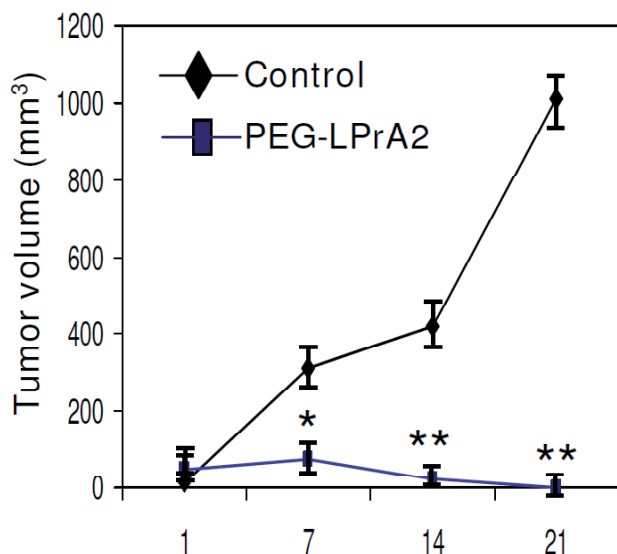


Figure 1: Following establishment of MCF-7 tumours mice were allocated to treatment or control groups. Treatment consisted of intravenous injection of the pegylated leptin receptor antagonist peptide every 2nd day for 18 days.

Encouragingly, administration of the peptide at the effective dose used in the tumour models produced no observable toxicity and had no adverse effect on food intake or body weight (6).

These data provide good evidence that interfering with the leptin signalling pathway may represent a novel and effective strategy for therapeutic intervention in breast cancers.

Successful peptide optimisation studies are ongoing and peptide antagonists with even greater activity than LPA-2 have been generated.

Other Indications: Endometriosis

Endometriosis results from inappropriate growth of endometrial tissue outside of the womb. It is a very common condition and may affect up to 10-15% of women during their reproductive years. Although the growths are normally benign this condition causes considerable discomfort and lifestyle issues for many women and there are currently no curative treatments available. The inventors have tested

the leptin antagonistic peptides in an *in vivo* murine model of endometriosis and shown that the peptides inhibit the proliferation of ectopic endometrial lesions and associated angiogenesis (7). Leptin antagonists may therefore represent a promising new therapeutic strategy for targeting this widespread disease.

Intellectual Property

Granted patent US7407929.
US divisional application US12/157,127.

Commercial Opportunity

CRT is currently seeking a commercial partner to take on the development of this technology under an exclusive license agreement.

References

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- (4) A peptide derived from the human leptin molecule is a potent inhibitor of the leptin receptor function in rabbit endometrial cells. Gonzalez and Leavis, Endocrine. 2003 21:185-195
- (5) Leptin signalling promotes the growth of mammary tumours and increases the expression of vascular endothelial growth factor (VEGF) and its receptor type two (VEGF-R2). Gonzalez *et al.*, J Biol Chem. 2006 281:26320-26328
- (6) Leptin-signalling inhibition results in efficient anti-tumour activity in estrogen receptor positive or negative breast cancer Gonzalez *et al.*, Breast Cancer Res. 2009 Pubmed ID: 19531256
- (7) Ablation of leptin signalling disrupts the establishment, development and maintenance of endometriosis-like lesions in a murine model. Styer *et al.*, Endocrinology. 2008. 149:506-514.

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